REMARKS

By this amendment, claims 1, and 6-8 have been amended. Support for these amendments can be found in the specification at page 12, line 26, to page 13, line 21; page 18, lines 5-14, page 7, line 25, and page 10, lines 15-31.

Restriction of Previously-submitted Claims 9-24

The Examiner contends that previously-submitted claims 9-34 are directed to an invention that is distinct or independent from the originally claimed invention since these claims are drawn to distinct species of target, proteins, or modifiers which were not elected. The Examiner acknowledges that claim 1 is a genus claim and claims 9-24 are species thereof.

In response to this statement, Applicants will withdraw these claims from consideration. However, Applicants request that, should generic claim 1 be allowable following this submission, the claims will be withdrawn from consideration and the Examiner will make species election requirement pursuant to MPEP section 809.02(b), followed by a full action on the merits for the elected species.

Claim Rejections Under 35 U.S.C. §102(b)-Anticipation

The Examiner maintains his rejection of claim 1, and further rejects previously added claims 6 and 7, as allegedly anticipated by Li et al., *PNAS USA* 1997; 94: 73-78 ("Li"). The Examiner contends that Li discloses a method for identifying a compound that inhibits the CDR/MHC class II interaction that is identical to the method recited in the present claims. The Examiner did not find our previous arguments to be persuasive, namely that Li does not disclose a method for identifying a modulatory compound for an allosteric cavity that is proximal to the active site.

As asserted in the previous response, filed June 11, 2003, Li discloses a computer-based strategy for identifying compounds that bind to a functionally critical site on the surface of CD4. This binding site is defined by Li as the site where the CD4 receptor interacts (*i.e.*, binds) with the MHC II antigen on the antigen-presenting cell (see page 74, column 1). This site is clearly not the same as the proximal, allosteric

site as defined in the present claims, and, to clarify this distinction, claim 1 has been amended herein to recite that this proximal site (*i.e.*, proximal cavity) is within a flexible region of the target protein which also comprises the functionally critical site, but is located about 15-20 Ångstroms away from the functionally critical site, and that binding of a compound at this proximal site modulates binding of another ligand at the functionally critical site (as determined from an estimation of conformational perturbance). Support for the term "flexible" in the amendment is found in the specification at page 10, lines 11-31, which describes that functionally critical sites of proteins are flexible in order to accommodate binding by a biological ligand. Support for this is also found on page 9, lines 6-11, which defines a proximal cavity by its ability to *alter* a functionally critical site when there is a modifier bound in the proximal cavity. Similarly, by definition (according to Merriam-Webster's Online Dictionary), the term "allosteric" means "of, relating to, or being a *change in the shape* and activity of a protein that results from combination with another substance at a point other than the...active site" Lastly, page 7 defines the term "intermolecular interactions" as interactions which occur between a target and a modifier which include associateion, oligomerization, binding and *conformational/structural perturbances*.

In the Methods section on page 74, Li refers to an article published in 1990 by Ryu et al. that describes the high-resolution X-ray structure of the human CD4 D1 domain (see Exhibit A). According to the Ryu article, "residues implicated in HIV recognition by analysis of mutants and antibody binding are salient features in domain D1" (see abstract). Specifically, Li indicates that the large surface area of CD4 D1, and specifically loops designated FG and C'C", are particularly implicated in direct interaction with MHC II. Accordingly, the recognition-site in domain D1 of CD4 is a functionally critical site, *i.e.*, a site involved in direct interaction with a ligand. It can thus be inferred that the compounds identified by Li disrupt the CD4/MHC interaction by a competitive mechanism, *i.e.*, the compounds bind in the functionally critical site and block binding between the natural ligand and the receptor. This is supported by Li's statement on page 74 that his proposed binding-pocket was consistent with the available mutational data by Fleury et al. (see abstract at Exhibit B) that the CDR-MHC

interaction occurs at an epitope comprising amino acid residues 19, 89 and 165 on exposed loops of domain D1. This is further supported by Li's statement that the four disclosed inhibitors inhibit the CD4-MHC II interaction in a concentration-dependent manner (see page 75-76, bridging sentence), which is characteristic of competitive inhibition and not allosteric inhibition. Moreover, in the discussion on page 77 (column 2), Li states that:

> ...we have proposed that the CC' loop, together with the FG (CDR3) loop, form a critical binding pocket on the lateral surface of CD4. It is interesting to note that similar surface pockets on other Ig-related proteins are also involved in molecular interactions and biological functions *(emphasis supplied)*...a similar pocket consisting of the FG and CC' loops is commonly observed to be involved in dimerization of Ig superfamily molecules...this pocket also mediates heterophilic interactions ...The results of our study regarding the role of the CD4 surface pocket in mediating stable MHC class II interaction and T-cell activation are consistent with this notion.

Taken together, the above statements made by Li support that his disclosed inhibitors bind in a functionally critical site and not an allosteric site.

Regarding the Examiner's allegations that the two state-of-the-art references by Piater-Tonneau and Coffin (Piatier-Tonneau et al., *Immunogenetics* 1991; 34: 121-28; and Coffin et al., Retroviruses at the National Center for Biotechnology Information) disclose the inherent characteristics of CD4, and therefore, support anticipation of the claims by Li, Applicants respectfully request the Examiner to consider the following remarks. First, Piatier-Tonneau discloses the fact that not all anti-CD4 antibodies inhibit HIV-blocking activity (*i.e.*, inhibit MHC II-dependent gp120 binding to T cells), and, as such, suggests a model wherein joint binding of MHC class II molecules, CD4 and the TCR occurs. In other words, a model where binding of CD4 to the TCR induces a conformational change which then enables MHC binding (or some combination thereof). However, this differs from the "allosteric" mediator of the present claims, since the sites of interaction of CDR/TCR/MHC are still "functional"

binding sites since binding of both CD4 positive T cells and MHC antigens are required for function, *i.e.*, antigen presentation and an ensuing immune response. This reference does not teach or suggest an additional, allosteric cavity which is located about 15-20 Ångstroms distant from these binding sites.

Second, Applicants are unsure of the purpose for the Coffin citation, which discloses only that CD4 has multiple domains. This is true of every protein, and is irrelevant to the patentability of the present claims, which require that an allosteric modulator bind in a flexible region containing an appropriate cavity proximal to the functional interface (*i.e.*, CD4/MHC interface), and not at a functional interface.

Claim Rejections Under 35 U.S.C. §112-Enablement

The Examiner maintains his rejection of claim 1 for lack of enablement. According to the Examiner, practicing the claimed screening method depends upon first obtaining a known *crystal structure* of the target protein.

The test for enablement is not determined by whether the state of the art (at the time the application was filed) enabled the claims, but involves a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable *one skilled in the pertinent art* to make and use the claimed invention. Specifically, the Court of Appeals for the Federal Circuit interpreted the test for compliance with the enablement requirement:

> ...whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See *In re Wands* 858 F.2d 737; 8 USPQ2d 1404.

The law determines "undue experimentation" according to a set of factors including the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity

of experimentation needed to make or use the invention based on the content of the disclosure. See M.P.E.P. §2164.01(a). Further, it is improper come to a conclusion of non-enablement based on analysis of only *one* of the preceding factors.

The law further states that an extended period of experimentation may not be "undue" experimentation if the skilled artisan is given sufficient direction or guidance. See *In re Colianni* 561 F2d.220, 224; 195 USPQ 150, 153 (CCPA 1977).

In view of the law cited above, Applicants do not find this rejection well-founded and respectfully traverse the rejection. Contrary to the Examiner's interpretation, the claims are not directed to identifying three-dimensional structures of proteins, much less by obtaining their crystal structures. The claims are directed to a screening method, which presumes that a three-dimensional structure is available for the target protein (as elucidated by ANY method, including computer modeling using algorithms, and any viable method not yet discovered), and which does not depend on identifying the structure in order to practice. The method, which was enabled at the time of filing, will work equally well for a target protein whose three-dimensional structure was known at the time of filing, whose structure was determined the next day, and for yet-unidentified proteins whose structure will be determined.

In support of this assertion, note that numerous patents have issued with claims directed towards general screening methods and other methods that are applicable to genes or proteins or compounds that will come into existence a later date. Some recently issued claims are as follows:

PATENT NO.	EFFECTIVE FILING: ISSUE DATE	CLAIM
6,627,453	3/27/98: 9/3/03	1. A method for ***screening*** a compound library to determine the relative affinity of a plurality of putative ligands to a target receptor relative to an indicator compound having a pre-determined affinity for the target receptor, which method comprises: (a) providing a compound library comprising a plurality of putative ligands; (b) providing at least one void marker compound;

		(c) providing a column comprising a target receptor selected from the group consisting of peptides, proteins, glycoproteins, glycosaminoglycans, proteoglycans, integrins, enzymes, lectins, selecting, cell-adhesion molecules, toxins, transport proteins, hormones, antibodies, cadherins, DNA, DNA fragments, RNA and RNA fragments optionally immobilized on a solid phase support; (d) providing an indicator compound having a pre-determined affinity for the target receptor and having a pre-determined break through time on said column in the absence of the compound library relative to said void marker compound and having a pre-determined signal intensity in the presence of the compound library; (e) applying a mixture comprising the compound library and the indicator compound to the column under frontal chromatography conditions to provide an effluent; (f) analyzing the effluent to determine a break through time and/or signal intensity for the indicator compound, and (g) determining whether any putative ligands of the compound library have an affinity for the target receptor by comparing the break through time for the indicator compound from step (f) with the pre-determined break through time for the indicator compound in the absence of the compound library.
6,566,079	2/2/98: 5/30/03	1. A method of ***screening*** ligands for the ability to bind to a ***protein*** of interest, comprising: (a) contacting said ***protein*** of interest with a ligand, wherein said ***protein*** of interest or said ligand is contained within a molecular binding region which is electromagnetically coupled to a portion of a signal path, said signal path operable to support a signal propagated at one or more frequencies in the range from 10 MHz to 1000 GHz and comprising a waveguide or resonant cavity; and (b) detecting a response signal at one or more frequencies in said range from 10 MHz to 1000 GHz indicating a binding complex formed between said ***protein*** of interest and said ligand, wherein said response signal results from coupling of said propagated signal to said ***protein,*** said ligand, or said complex
6,261,772	1/20/98:7/17/01	1. A method for ***screening*** a test compound for its ability to modulate a RNA:protein interaction

		comprising: i) preparing a reporter construct comprising, in order, a Tat-responsive promoter operably linked to a sequence encoding a heterologous RNA binding site, and an indicator gene, ii) preparing an effector construct comprising a promoter operably linked to a nucleic acid sequence encoding a fusion ***protein*** comprising a Tat ***protein*** activation domain and a ***protein*** cognate of said heterologous RNA binding sites, iii) introducing said reporter construct and said effector construct into a vertebrate host cell and culturing said host cell in the presence and absence of said test compound, and iv) measuring the level of expression of said indicator gene in the presence and absence of said test compound, a difference in the level of expression of said indicator gene in the presence of said test compound, as compared to the level of expression of said indicator gene in the absence of said test compound, being indicative of a test compound that modulates interaction of said heterologous RNA binding site with said ***protein*** cognate.

Regarding the '453 patent above, Applicants note that the specification does not describe or provide sequences for every protein in each of the categories listed in part (c) of the claim. Similarly, the compound libraries, ligands, test compounds, and proteins of interest recited in the tabulated claims similarly obviously include compounds, ligands and proteins that were not yet discovered at the time these applications were filed.

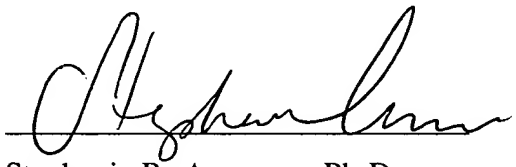
In addition, patents have also issued with claims directed to methods of producing transgenic/knock-out mice (see, *e.g.*, 6,548,740 directed to a method of producing transgenic cows; and 6,498,285 directed to a method of producing transgenic pigs). These claims were presumably enabled as of the filing date with the described gene, and the PTO evidently did not require the inventors to enable identification and cloning of every yet unidentified gene that could be employed in the claimed method at time the application was filed.

fact that the present claims are not even directed to identifying 3-dimensional structures of proteins, it is emphatically asserted that the claimed method is enabled for any protein for which a 3-dimensional structure is presently known, or will be known, using any method available.

Therefore, in view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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Second, despite the Examiner's insistence that determining three dimensional structure remains an unpredictable art, and requires "undue" experimentation, Applicants previously pointed out the fact that over 3500 proteins from over 2526 biological macromolecules have been crystallized as of 1998-(see Exhibit 4 filed with the response dated June 11, 2003), which is now more than 5 years ago. Further, the Protein Data Bank (www.rscb.org/pdb/) maintained through a collaboration of 4 institutions, contains 27,392 structures that have been determined by X-ray diffraction (crystallization), NMR or other techniques as of December 2003.
Applicants also submitted Exhibits 1-5 in the previous response regarding the advances in protein structure prediction that were made using knowledge-based and computer-based methods.

Third, the Examiner is incorrect in citing the Examples, which rely crystal structures, as the only enablement for the claimed invention. There is no statutory requirement for the presence of specific examples, and although the examples *may* represent the "best mode" of the invention, they are not preclusive to claiming other, unexemplified embodiments as long as the embodiments are sufficiently described and enabled.

Accordingly, given that structures of thousands of proteins were known at the time of filing (*e.g.*, the state of the prior art); the level of one of ordinary skill in protein prediction was high (as evidenced by the previously-submitted documents, and the teachings in the specification); the level of predictability in the art (*e.g.*, regarding facile prediction of the structures of homologous proteins) is high; the amount of direction provided by the inventor in the specification is sufficient; the existence of working examples (there are 3 in this application); it is respectfully asserted that any experimentation required to practice the claimed method is not "undue".

Therefore, given the advanced state of the art, and the likelihood that proteins discovered in the future will have a certain level of homology with at least one protein whose structure is known, or was known at the time of filing, it is respectfully asserted that identifying 3-dimensional structures of proteins whose primary amino acid sequence is known does not require undue experimentation. Taken together with the